

## AMENDMENTS TO THE SPECIFICATION:

Please replace the title of the application on page 1 with the following title:

NOVEL ~~POLYPEPTIDES~~ ENDOZEPINE-RELATED PRECURSOR LIKE  
PROTEINS AND NUCLEIC ACIDS ENCODING SAME

Please replace the first paragraph on page 1, starting with "This application claims ..." with the following amended paragraph:

This application is a continuation-in-part application of U.S.S.N. 10/035,568, filed October 22, 2001, which claims ~~priority from~~ benefit of U.S.S.N. 60/242,485 (21402-175), filed October 23, 2000; U.S.S.N. 60/263,339 (21402-175A), filed January 22, 2001; and U.S.S.N. 60/264,850 (21402-175B), filed January 29, 2001 ~~and U.S.S.N. 10/035,568, filed October 22, 2001~~, each of which is incorporated by reference in its entirety.

Please replace the paragraph on page 8, lines 16-30, beginning with "The Expect value is ..." with the following amended paragraph:

The Expect value is used as a convenient way to create a significance threshold for reporting results. The default value used for blasting is typically set to 0.0001. In BLAST 2.0, the Expect value is also used instead of the P value (probability) to report the significance of matches. For example, an E value of one assigned to a hit can be interpreted as meaning that in a database of the current size one might expect to see one match with a similar score simply by chance. An E value of zero means that one would not expect to see any matches with a similar score simply by chance. See, *e.g.*, the National Center for Biotechnology Information ("NCBI") website regarding the BLAST information (education/blastinfo) <http://www.ncbi.nlm.nih.gov/Education/BLASTinfo/>. Occasionally, a string of X's or N's will result from a BLAST search. This is a result of automatic filtering of the query for low-complexity sequence that is performed to prevent artifactual hits. The filter substitutes any low-complexity sequence that it finds with the letter "N" in nucleotide sequence (e.g., "NNNNNNNNNNNNNN") or the letter "X" in protein sequences (e.g., "XXXXXXXXXX"). Low-complexity regions can result in high scores that reflect compositional bias rather than significant position-by-position alignment. (Wootton and Federhen, Methods Enzymol 266:554-571, 1996).

Please replace the paragraph on page 11, lines 58-68, beginning with “The presence of identifiable ...” with the following amended paragraph:

The presence of identifiable domains in NOV1 was determined by searches using software algorithms such as PROSITE, DOMAIN, Blocks, Pfam, ProDomain, and Prints, and then determining the Interpro number by crossing the domain match (or numbers) using the Interpro website (<http://www.ebi.ac.uk/interpro>). DOMAIN results for NOV1 as disclosed in Tables 1F, were collected from the Conserved Domain Database (CDD) with Reverse Position Specific BLAST analyses. This BLAST analysis software samples domains found in the Smart and Pfam collections. For Table 1F and all successive DOMAIN sequence alignments, fully conserved single residues are indicated by black shading or by the sign (!) and “strong” semi-conserved residues are indicated by grey shading or by the sign (+). The “strong” group of conserved amino acid residues may be any one of the following groups of amino acids: STA, NEQK, NHQK, NDEQ, QHRK, MILV, MILF, HY, FYW.

Please replace the paragraph on page 13, lines 12-26, beginning with “The Expect value is ...” with the following amended paragraph:

The Expect value is used as a convenient way to create a significance threshold for reporting results. The default value used for blasting is typically set to 0.0001. In BLAST 2.0, the Expect value is also used instead of the P value (probability) to report the significance of matches. For example, an E value of one assigned to a hit can be interpreted as meaning that in a database of the current size one might expect to see one match with a similar score simply by chance. An E value of zero means that one would not expect to see any matches with a similar score simply by chance. See, *e.g.*, [the NCBI website regarding the BLAST information \(education/blastinfo\)](http://www.ncbi.nlm.nih.gov/education/blastinfo/)

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Please replace the paragraph on page 15, lines 4-14, beginning with “The presence of identifiable ...” with the following amended paragraph:

The presence of identifiable domains in NOV2a was determined by searches using software algorithms such as PROSITE, DOMAIN, Blocks, Pfam, ProDomain, and Prints, and then determining the Interpro number by crossing the domain match (or numbers) using the Interpro website (<http://www.ebi.ac.uk/interpro>). DOMAIN results for NOV2a and its variants as disclosed in Table 30, were collected from the Conserved Domain Database (CDD) with Reverse Position Specific BLAST analyses. This BLAST analysis software samples domains found in the Smart and Pfam collections. For Table 30 and all successive DOMAIN sequence alignments, fully conserved single residues are indicated by black shading or by the sign (!) and “strong” semi-conserved residues are indicated by grey shading or by the sign (+). The “strong” group of conserved amino acid residues may be any one of the following groups of amino acids: STA, NEQK, NHQK, NDEQ, QHRK, MILV, MILF, HY, FYW.

Please replace the paragraph on page 38, lines 1-6, beginning with “The disclosed NOV1 protein ...” with the following amended paragraph:

The disclosed NOV1 protein of the invention includes the endozepine-related protein precursor-like protein whose sequence is provided in Table 1B. The invention also includes a mutant or variant protein any of whose residues may be changed from the corresponding residue shown in Table 1B while still encoding a protein that maintains its endozepine-related protein precursor -like activities and physiological functions, or a functional fragment thereof. In the mutant or variant protein, up to about 60% ~~percent~~ of the residues may be so changed.

Please replace the paragraph on page 113, line 25, to page 114, line 9, beginning with “To prepare the primary ...” with the following amended paragraph:

To prepare the primary and secondary Th1/Th2 and Tr1 cells, six-well Falcon plates were coated overnight with 10  $\mu$ g/ml anti-CD28 (Pharmingen) and 2  $\mu$ g/ml OKT3 (ATCC), and then washed twice with PBS. Umbilical cord blood CD4 lymphocytes (Poietic Systems, German Town, MD) were cultured at  $10^{-5}$   $10^{-6}$  cells/ml in DMEM 5% FCS (Hyclone), 100  $\mu$ M non essential amino acids (Gibco), 1 mM sodium pyruvate (Gibco), mercaptoethanol  $5.5 \times 10^{-5}$  M (Gibco), 10 mM Hepes (Gibco) and IL-2 (4 ng/ml). IL-12 (5 ng/ml) and anti-IL4 (1

~~1 µg/ml~~ 1 µg/ml) were used to direct to Th1, while IL-4 (5 ng/ml) and anti-IFN gamma (1 ~~1 µg/ml~~ 1 µg/ml) were used to direct to Th2 and IL-10 at 5 ng/ml was used to direct to Tr1. After 4-5 days, the activated Th1, Th2 and Tr1 lymphocytes were washed once in DMEM and expanded for 4-7 days in DMEM 5% FCS (Hyclone), 100 µM non essential amino acids (Gibco), 1 mM sodium pyruvate (Gibco), mercaptoethanol  $5.5 \times 10^{-5}$  M (Gibco), 10 mM Hepes (Gibco) and IL-2 (1 ng/ml). Following this, the activated Th1, Th2 and Tr1 lymphocytes were re-stimulated for 5 days with anti-CD28/OKT3 and cytokines as described above, but with the addition of anti-CD95L (1 µg/ml) to prevent apoptosis. After 4-5 days, the Th1, Th2 and Tr1 lymphocytes were washed and then expanded again with IL-2 for 4-7 days. Activated Th1 and Th2 lymphocytes were maintained in this way for a maximum of three cycles. RNA was prepared from primary and secondary Th1, Th2 and Tr1 after 6 and 24 hours following the second and third activations with plate bound anti-CD3 and anti-CD28 mAbs and 4 days into the second and third expansion cultures in Interleukin 2.